PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

MAIWALD, Walter
Maiwald GmbH
Elisenhof
Elisenstrasse 3
D-80335 München
ALLEMAGNE

MAIWALD
Patentanwalts-GmbH
12. Sep. 2000
MÜNCHEN

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	08.09.2000
Applicant's or agent's file reference M 7708/WM	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/03681	27/05/1999	27/05/1998

Applicant
EUOROCELTIQUE S.A.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Tantum, P Tel.+49 89 2399-8143

Form PCT/IPEA/416 (July 1992)

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
M 7708/WM		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/03681	27/05/1999	27/05/1998
International Patent Classification (IPC) or national classification and IPC A61K9/127		
Applicant EUOROCELTIQUE S.A.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13/11/1999	08.09.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Pregetter, M Telephone No. +49 89 2399 8719

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/03681

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-20 as originally filed

Claims, No.:

1-43 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 22-43 concerning industrial applicability.

because:

☒ the said international application, or the said claims Nos. 22-43 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-43
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-43
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-21
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 22-43 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following document:

   D2: GILBERT BE, WYDE PR, WOLSON ST: 'Aerosolized liposomal amphotericin B for treatment of pulmonary and systemic Cryptococcus neoformans infections in mice', ANTIMICROB. AGENTS CHEMOTHER.,vol. 36, no. 6, pages 1466-1471, 1992.

2.1. Document D2, which is considered to represent the most relevant state of the art, discloses (cf. abstract) a process for the manufacture of a pharmaceutical preparation suitable for administration to the lower respiratory tract from which the subject-matter of claim 1 differs in that an antiseptic agent and/or an agent which promotes the healing of wounds is used instead of an antibiotic as disclosed in D2.

The subject-matter of claim 1 is therefore novel (Article 33(2) PCT).

2.2. The problem to be solved by the present invention may therefore be regarded as: How to manufacture a pharmaceutical preparation for the application of an antiseptic and/or an agent which promotes the healing of wounds to the lower respiratory tract.

2.3. The solution to this problem proposed in claim 1 of the present application is

considered as involving an inventive step (Article 33(3) PCT) for the following reasons:
None of the documents cited in the search report describe or even suggest to use antiseptic or wound healing substances for the treatment of infections of the human or animal lower respiratory tract. Consequently, there is no incentive for a person skilled in the art to try and manufacture a pharmaceutical preparation comprising an antiseptic and/or wound healing substance for the treatment of the lower respiratory tract.

2.4. Claims 2-21 are dependent on claim 1 and as such also meet the requirements of the PCT with respect to novelty and inventive step.

3. The same reasoning as in point 2. applies to claims 22-43.

4. For the assessment of the present claims 22-43 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

1. The term "about" used in claims 9, 10, 17, 18, 32, 33, 40, 41 in connection to a range is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

ATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

MAIWALD, Walter
Maiwald GmbH
Elisenhof
Elisenstrasse 3
D-80335 München
ALLEMAGNE

MAIWALD
Patentanwalts-GmbH
12. April 2000
MÜNCHEN
EINGANG 10.07.N 16

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	10.04.2000
Applicant's or agent's file reference: M 7708/WM	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/03681	27/05/1999	27/05/1998

International Patent Classification (IPC) or both national classification and IPC

A61K9/127

Applicant

EUOROCELTIQUE S.A.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 27/09/2000.

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner
Pregetter, M

Formalities officer (incl. extension of time limits)
Tantum, P
Telephone No. +49 89 2399 8143

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-20 as originally filed

Claims, No.:

1-43 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 22-43 concerning industrial applicability,

because:

☒ the said international application, or the said claims Nos. 22-43 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims. or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-3, 9, 15, 16, 19, 20, 22, 24- 26, 32, 38, 39, 42, 43
Inventive step (IS)	Claims	1-3, 9, 11, 12, 14-16, 19, 20, 24-26, 32, 34, 35, 37-39, 42, 43
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 22-43 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1.1. Reference is made to the following documents:

D1: EP-A-0 639 373 (EUROCELTIQUE) 22 February 1995 (1995-02-22)

1.2. The following document (D) is cited by the examiner. A copy of the document is annexed to the communication and the numbering will be adhered to in the rest of the procedure:

D2: GILBERT BE, WYDE PR, WOLSON ST: 'Aerosolized liposomal amphotericin B for treatment of pulmonary and systemic Cryptococcus neoformans infections in mice', ANTIMICROB. AGENTS CHEMOTHER.,vol. 36, no. 6, pages 1466-1471, 1992.

2. The subject-matter of claims 1 and 22 are not new according to article 33(2) PCT. Document D2 discloses a liposome composition comprising an antiseptic agent (amphotericin B).
Document D2 uses the liposomal preparations of amphotericin B to fight pulmonary infections with *Cryptococcus neoformans*.

3. The dependent claims 2, 3, 9, 15, 16, 19, 20, 24, 25, 26, 32, 38, 39, 42, 43 and 44 contain additional technical features which might establish novelty over D2 (article 33(2) PCT). Dependent claims are only allowable in combination with patentable

independent claims.

4. The dependent claims 11, 12, 14, 34, 35, 37, do not contain additional technical features which might establish an inventive step over D1 (article 33(3) PCT). If certain release properties are desirable (cf. claims 11, 12, 34, 35), a person skilled in the art would simply use a liposomal system with these properties, as discloses in D1. Concerning the addition of additives (claims 14, 37): It is well known that liposomal systems, which are destined for pharmaceutical or cosmetic use (not only for research purposes), must include additives for stabilisation and to acquire the necessary physical form.

5. For the assessment of the present claims 22-43 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII
Certain observations on the international application

1. The term "about" used in claims 9, 10, 17, 18, 32, 33, 40, 41 in connection to a range is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

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Europäisch s Patentamt
Generaldirektion 2

Europ an Patent Office
Directorate General 2

Office européen d s brevets
Direction Générale 2

Correspondence with the EPO on PCT Chapter II demands

In order to ensure that your PCT Chapter II demand is dealt with as promptly as possible you are requested to use the enclosed self-adhesive labels with any correspondence relating to the demand sent to the Munich Office.

One of these labels should be affixed to a prominent place in the upper part of the letter or form etc. which you are filing.

15

PATENT COOPERATION TREATY

PCT

REC'D 13 SEP 2000
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
M 7708/WM		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/03681	27/05/1999	27/05/1998
International Patent Classification (IPC) or national classification and IPC A61K9/127		
Applicant EUOROCELTIQUE S.A.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13/11/1999	08.09.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 39 2399 - 4465	Authorized officer Pregetter, M Telephone No. +49 89 2399 8719

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/03681

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-20 as originally filed

Claims, No.:

1-43 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 22-43 concerning industrial applicability.

because:

☒ the said international application, or the said claims Nos. 22-43 relate to the following subject matter which does not require an international preliminary examination (*specify*):

s separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-43
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-43
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-21
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 22-43 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following document:

   D2: GILBERT BE, WYDE PR, WOLSON ST: 'Aerosolized liposomal amphotericin B for treatment of pulmonary and systemic Cryptococcus neoformans infections in mice', ANTIMICROB. AGENTS CHEMOTHER.,vol. 36, no. 6, pages 1466-1471, 1992.

2.1. Document D2, which is considered to represent the most relevant state of the art, discloses (cf. abstract) a process for the manufacture of a pharmaceutical preparation suitable for administration to the lower respiratory tract from which the subject-matter of claim 1 differs in that an antiseptic agent and/or an agent which promotes the healing of wounds is used instead of an antibiotic as disclosed in D2.

The subject-matter of claim 1 is therefore novel (Article 33(2) PCT).

2.2. The problem to be solved by the present invention may therefore be regarded as: How to manufacture a pharmaceutical preparation for the application of an antiseptic and/or an agent which promotes the healing of wounds to the lower respiratory tract.

2.3. The solution to this problem proposed in claim 1 of the present application is

considered as involving an inventive step (Article 33(3) PCT) for the following reasons:
None of the documents cited in the search report describe or even suggest to use antiseptic or wound healing substances for the treatment of infections of the human or animal lower respiratory tract. Consequently, there is no incentive for a person skilled in the art to try and manufacture a pharmaceutical preparation comprising an antiseptic and/or wound healing substance for the treatment of the lower respiratory tract.

2.4. Claims 2-21 are dependent on claim 1 and as such also meet the requirements of the PCT with respect to novelty and inventive step.

3. The same reasoning as in point 2. applies to claims 22-43.

4. For the assessment of the present claims 22-43 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

1. The term "about" used in claims 9, 10, 17, 18, 32, 33, 40, 41 in connection to a range is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

RH

ATENT COOPERATION TREA

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
M 7708		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 99/ 03681	27/05/1999	27/05/1998
Applicant		
EUOROCELTIQUE S.A.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   PREPARATIONS FOR THE APPLICATION OF ANTI-INFLAMMATORY, ESPECIALLY ANTISEPTIC AGENTS AND/OR AGENTS PROMOTING THE HEALING OF WOUNDS, TO THE LOWER RESPIRATORY TRACT

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from th date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with th abstract is Figure No. —

   [ ] as suggested by th applicant.

   [ ] because th applicant failed to suggest a figure.

   [ ] because this figure better characterizes th invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/03681

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 22-43 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied th payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/03681

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/127

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 639 373 A (EUROCELTIQUE) 22 February 1995 (1995-02-22) claims 1-18	1-43
A	EP 0 613 685 A (GONZALEZ ENSENAT, PEDRO, ET AL.) 7 September 1994 (1994-09-07) claim 1 column 4, line 19 - line 26	1-43
A	EP 0 509 338 A (MERZ & CO.) 21 October 1992 (1992-10-21) claims 1,9 example 7	1-43

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 October 1999	09/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Ventura Amat, A

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/03681

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 117, no. 10, 7 September 1992 (1992-09-07) Columbus, Ohio, US; abstract no. 97244, GILBERT, BRIAN E. ET AL: "Aerosolized liposomal amphotericin B for treatment of pulmonary and systemic Cryptococcus neoformans infections in mice" XP002119931 abstract & ANTIMICROB. AGENTS CHEMOTHER. (1992), 36(7), 1466-71 ,1992,	1-3, 9-12, 14-16, 18-26, 32-35, 37-39, 41-43

2

INTERNATIONAL SEARCH REPORT

ation on patent family members

International Application No
PCT/EP 99/03681

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 639373 A	22-02-1995	DE 9312509 U	28-10-1993
		AT 173917 T	15-12-1998
		DE 69414936 D	14-01-1999
		DE 69414936 T	12-08-1999
		ES 2124822 T	16-02-1999
		GR 3029436 T	28-05-1999
		JP 7145081 A	06-06-1995
		SI 639373 T	30-04-1999
		US 5863556 A	26-01-1999
EP 613685 A	07-09-1994	DE 4306475 A	08-09-1994
		AT 173158 T	15-11-1998
		DE 59407247 D	17-12-1998
		ES 2124328 T	01-02-1999
EP 509338 A	21-10-1992	DE 4111982 A	15-10-1992
		AT 126430 T	15-09-1995
		CA 2065579 A	13-10-1992
		DE 59203259 D	21-09-1995
		DK 509338 T	18-09-1995
		ES 2077904 T	01-12-1995
		GR 3017147 T	30-11-1995
		JP 7048247 A	21-02-1995
		US 5498420 A	12-03-1996

PATENT COOPERATION TREA

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
MAIWALD GMBH
Elisenhof
Elisenstrasse 3
D-80335 München
GERMANY

Date of mailing *(day/month/year)* 09/11/1999	
Applicant's or agent's file reference M 7708	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/EP 99/03681	International filing date *(day/month/year)* 27/05/1999
Applicant EUOROCELTIQUE S.A.	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet. a14 = 9.1.00

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Barbara Klaver

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREA

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
M 7708		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 99/ 03681	27/05/1999	27/05/1998
Applicant		
EUOROCELTIQUE S.A.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

PREPARATIONS FOR THE APPLICATION OF ANTI-INFLAMMATORY, ESPECIALLY ANTISEPTIC AGENTS AND/OR AGENTS PROMOTING THE HEALING OF WOUNDS, TO THE LOWER RESPIRATORY TRACT

5. With regard to the **abstract**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. --

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/03681

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 22-43 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/03681

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/127

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 639 373 A (EUROCELTIQUE) 22 February 1995 (1995-02-22) claims 1-18 ---	1-43
A	EP 0 613 685 A (GONZALEZ ENSENAT, PEDRO, ET AL.) 7 September 1994 (1994-09-07) claim 1 column 4, line 19 - line 26 ---	1-43
A	EP 0 509 338 A (MERZ & CO.) 21 October 1992 (1992-10-21) claims 1,9 example 7 ---	1-43

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 October 1999	09/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Ventura Amat, A

2

Form PCT/ISA/210 (second sheet) (July 1992)

International Application No
PCT/EP 99/03681

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 117, no. 10, 7 September 1992 (1992-09-07) Columbus, Ohio, US; abstract no. 97244, GILBERT, BRIAN E. ET AL: "Aerosolized liposomal amphotericin B for treatment of pulmonary and systemic Cryptococcus neoformans infections in mice" XP002119931 abstract & ANTIMICROB. AGENTS CHEMOTHER. (1992), 36(7), 1466-71 ,1992,	1-3, 9-12, 14-16, 18-26, 32-35, 37-39, 41-43

INTERNATIONAL SEARCH REPORT

[redacted]mation on patent family members

[redacted]ternational Application No
[redacted]CT/EP 99/03681

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 639373 A	22-02-1995	DE 9312509 U	28-10-1993
		AT 173917 T	15-12-1998
		DE 69414936 D	14-01-1999
		DE 69414936 T	12-08-1999
		ES 2124822 T	16-02-1999
		GR 3029436 T	28-05-1999
		JP 7145081 A	06-06-1995
		SI 639373 T	30-04-1999
		US 5863556 A	26-01-1999
EP 613685 A	07-09-1994	DE 4306475 A	08-09-1994
		AT 173158 T	15-11-1998
		DE 59407247 D	17-12-1998
		ES 2124328 T	01-02-1999
EP 509338 A	21-10-1992	DE 4111982 A	15-10-1992
		AT 126430 T	15-09-1995
		CA 2065579 A	13-10-1992
		DE 59203259 D	21-09-1995
		DK 509338 T	18-09-1995
		ES 2077904 T	01-12-1995
		GR 3017147 T	30-11-1995
		JP 7048247 A	21-02-1995
		US 5498420 A	12-03-1996

MAIWALD PATENTANWALTS GMBH München · Hamburg

Patentanwälte

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Parr · Tauche · Jaeger ·
Leutheusser - Schnarrenberger
Rechtsanwälte
(München · Starnberg)

Europäisches Patentamt

80298 München

Application Number
PCT/EP99/03681
WO 99/60999
EUROCELTIQUE S.A.

Our Ref.
M 7708 / WM

Munich,
29 May 2000

Chapter II sticker

In response to the Written Opinion dated 10 April 2000, the following submission is made on behalf of the Applicant:

With respect to items 2 and 3 of the Written Opinion, the difference between the subject matter of the present invention and the cited document D2 will now be discussed in some detail.

In the Examiner's opinion, the subject matter of claims 1 and 22 is not new since D2 discloses a liposome composition comprising an antiseptic agent (amphotericin B). Moreover, the liposomal preparations according to D2 are used for the treatment of pulmonary infections with Cryptococcus species.

Claim 1 of the present invention is directed to the process for the manufacture of a pharmaceutical preparation for the application of antiseptic agents and/or agents which promote the healing of wounds to the lower respiratory tract, characterized in that the

WM:HG:sc

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Geschäftsführer: Dr. Walter Maiwald · Dr. Volker Hamm · Dr. Stefan Michalski - HRB Nr. 111307

preparation contains at least one of said agents combined with a particulate carrier. According to claim 22, a method of preventing or treating infections of the human or animal lower respiratory tract, by applying to said tract, a pharmaceutical preparation comprising at least one anticeptic agent and/or wound-healing promoting agent, whereby said agent is combined with a particulate carrier in said preparation is disclosed.

There is, by definition, a difference between an antiseptic agent and an antibiotic agent (and also between a wound-healing agent and an antibiotic agent).The use of antibiotic agents is definitely not intended and also not claimed in the present invention. On the contrary, the use of antibiotics is undesired according to the present invention. On page 2, lines 10 to 15 of the description, it is explicitly stated that the treatment with antibiotics leads to complications known to the skilled person and, moreover, antibiotics are inefficient for the treatment of diseases of the respiratory tract which are caused by viruses.

As can be taken from the description, e.g. on page 5, lines 6 to 15, antiseptic agents according to the present invention include inter alia, oxygen- and halogen-releasing compounds; metal compounds, organic disinfectants, alcohols, phenols etc. Wound healing agents according to the present invention preferably comprise agents promoting granulation and epithelization, such as dexpanthenol, allantoines, azulenes, tannines, and vitamin B-type compounds.

In document D2, a liposomal amphotericin B formulation for the treatment of pulmonary and systemic Cryptococcus neoformans infections is disclosed. D2 discloses a typical antibiotic use of amphotericin B, which is not an antiseptic agent within the common usage of this term. The agent amphotericin B is a well-known antibiotic agent, especially known as an effective antifungal agent. In order to leave no room for doubt that amphotericin B is an antibiotic agent or antifungal agent, document D3 is enclosed herewith.

Since the cited article (D2) is exclusively directed to liposomal amphotericin B, which is a typical antibiotic, and not an antiseptic agent, D2 does not anticipate the subject matter of claim 1 and 22 of the present application. Consequently, also the subject matter of the dependent claims is new.

In item 4 of the Written Opinion, it is stated that the dependent claims 11, 12, 14, 34, 35 and 37 do not contain additional technical features which might establish an inventive step over D1. Since these are just dependent claims, and their independent head claims are not touched by D1, this argument would appear moot.

It is agreed that D1 discloses liposomal formulations with certain release properties, especially preparations with protracted release properties. However, in this context it should be noted that D1 is directed to liposomal preparations for external application. According to the description of D1 on page 3, lines 29 to 31 and 44 to 48, suitable liposome preparations for external application can take a variety of forms, including solutions, dispersions, lotions, creams, ointments and gels, whereby the size of the liposomes is generally from about 20 to about 20,000 nm and preferably approximately 1000 nm in diameter. In contrast, the liposomal preparations according to the present invention take a variety of forms, which are suitable for administration via the lower respiratory tract, including pharmaceutically acceptable solid or liquid formulations, which are suitable for the generation of inhalable particles (page 11, lines 26-30). Accordingly, the carrier particles, especially liposomes, have very small sizes and range between about 1 and about 50 µm.

There is absolutely no doubt about the fact that there is a significant difference between the carrier particles according to the present invention and the liposome preparations according to D1, especially with respect to their specific features and also the manufacture of said particles. In other words, it is not possible to someone skilled in the art to simply transfer or

use the liposomal system according to D1, namely the creams and ointments, with certain release properties of the liposomal particles, in order to acquire a liposomal preparation according to the present invention, which is, for example, an aerosol, powder, powder aerosol, or a corresponding compacted solid medicament, as for example, a ring-tablet.

Therefore, the subject matter of claims 11, 12, 34, 35, as well as 14 and 37 is not obvious in view of the teaching of D1.

Finally, it is indicated that the term "about" has currently not been deleted from claims 9, 10, 17, 18 32, 33, 40 and 41; it should be acceptable in the present application, because it provides sufficient range when the term is used. The term "about" has to be seen as sufficiently definite when used in connection with the preferred range of the size of the carrier particles.

It is assumed that in view of the above explanations, the objections raised by the Examiner have been overcome.

Maiwald Patentanwalts-GmbH
(Walter Maiwald)

Encls:
Document D3.

Antifungals

An overview of the antifungals in current use or under development is geven by classifying the compounds by their mechanism of action. During recent years considerable advances have been made in the identification of potential targets for antifungal agents. Examples are listed in Table 21.2 (for a review see KERRIDGE and VANDEN BOSSCHE 1990). Although this table gives a variety of potential targets it is surprising that the clinically available antifungals interfere only with a limited number of targets. They either impair the membrane barrier function, inhibit ergosterol synthesis, inhibit macromolecular synthesis or prevent microtubule assembly.

Table 21.2 Examples of targets for antifungal agents

Organelles	Targets	Inhibitors
cell wall	chitinase	allosamidin
	glycosidases	castonospermine, deoxynojirimycin, bromoconduritol
plasma membrane	impairment of barrier function	polyenes (e.g. nystatin and amphotericin B)
		azole antifungals (high concentrations): miconazole, clotrimazole, propiconazole, penconazole, fluconazole
	chitin synthase(s)	polyoxins, nikkomycins
	β1,3-glucan synthase(s)	papulacandin, echinocandin, cilofungin
	mannoprotein synthesis	tunicamycin
	proton ATPase	miconazole (high concentrations)
endoplasmic reticulum	squalene epoxidase	naftifine, terbinafine, butenafine, tolnaftate, tolciclate
	P450-dependent 14α-demethylase	pyrimidine, pyridine, imidazole and triazole antifungals
	sterol Δ^{14}-reductase	morpholines (amorolfine)
	sterol $\Delta^{8} \rightarrow \Delta^{7}$-isomerase	morpholines
nucleus	nucleic acid synthesis	5-fluorocytosine
	microtubules	griseofulvin
cytosol	microtubules	griseofulvin
	ornithine decarboxylase	difluoromethylornithine (DFMO)

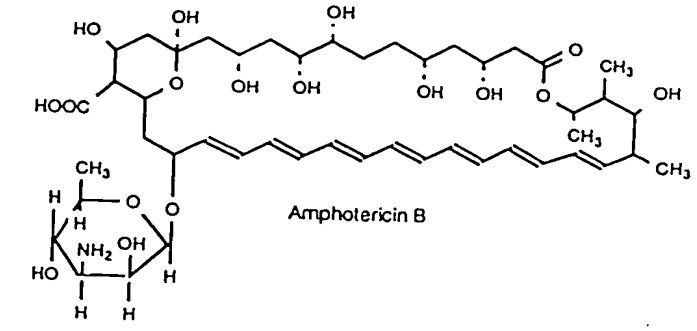
Compounds that impair the membrane barrier function

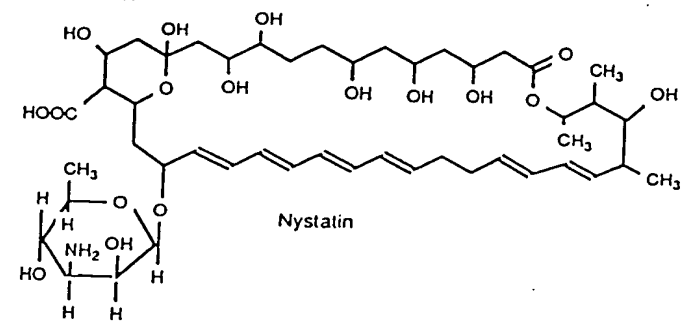
Polyenes

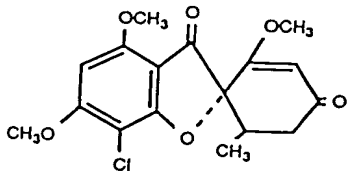
Polyene macrolide antibiotics, produced by species of *Streptomyces*, are characterized by large lactone rings, containing three to eight conjugated double bonds, which are generally combined with one sugar moiety. They can be subdivided into tetraenes (e.g.

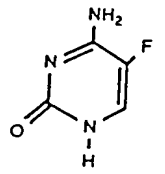
natamycin, nystatin), pentaenes (pentamycin) and the heptaenes (e. g. amphotericin B, candicidin). The chemical structures of amphotericin B and nystatin, are given in Fig. 21.1.

Both amphotericin B (AmB) and nystatin contain eight free hydroxyl groups in the macrocyclic lactone ring and possess as glycosidically linked carbohydrate moiety 3-amino-3,6-dideoxy-D-mannopyranose (mycosamine). These polyenes contain a hydrophobic and a hydrophilic chain, the latter contains the free hydroxyl groups, the former









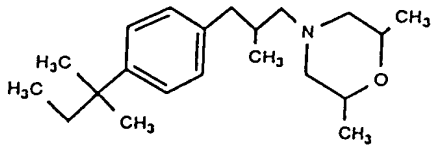


Fig. 21.1 Chemical structures of polyenes, griseofulvin, 5-fluorocytosine and amorolfine.

D 3

Modern Selective Fungicides

— Properties, Applications, Mechanisms of Action —

Editor

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(57) Abstract

Use of an anti-inflammatory agent such as povidone iodine for the preparation of a pharmaceutical composition for the treatment of diseases of the lower respiratory tract which are susceptible to the administration of such agents.

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Preparations for the application of anti-inflammatory, especially antiseptic agents and/or agents promoting the healing of wounds, to the lower respiratory tract

The invention concerns preparations for the application of agents with anti-inflammatory, especially antiseptic and/or wound healing promoting properties to the lower respiratory tract. The preparations are specifically applied to trachea, bronchi and alveoli in the lower respiratory tracts of humans and animals.

Furthermore, the invention concerns a method of preventing or treating infections by applying a pharmaceutical preparation.

A plurality of different antibiotic and antiseptic agents are known for the topical treatment of infectious maladies. A decisive disadvantage of antibiotic agents is that the infecting bacteria show primary resistances, and can acquire secondary resistances, against these agents. Further, antibiotics quite often lead to patient sensibilisation. The use of e.g. halogen-releasing antiseptics such as povidone iodine, also known as polyvidone iodine or PVP-iodine, i.e. the poly(1-vinyl-2-pyrrolidin-2-one)-iodine complex, can prevent resistances. Antiseptic agents are also much more rarely allergenic as compared to antibiotics.

At present, infectious diseases of the respiratory tract are treated with antibiotics. The application of antibiotic agents via the respiratory tract has been the subject of several reviews and articles with an emphasis on the lower respiratory tract. Ramsey et al., for example, describe the intermittent administration of inhaled tobramycin in patients with cystic fibrosis in "The New England Journal of Medicine", Volume 340, Number 1, 1999, p. 23-30.

The aerosolization of imipenem/cilastatin for preventing pseudomonas-induced acute lung injury has been investigated by Wiener-Kronish in "Journal of Antimicrobiol Chemotherapy" (1996) 38, p. 809-818.

Pulmonary applications of different antibiotic agents, like benzyl penicillin, tobramycin or amikacin, for the treatment of infectious diseases are described by Schreier in several recent reviews, e.g. in "Medical applications of liposomes", Papahadjopoulos and Lasic (eds.), Elsevier 1998.

However, the treatment with antibiotics leads to the complications known to the skilled person. For example, patients suffering from acute or chronic bronchitis are often treated with antibiotics in order to alleviate the symptoms. This often merely leads to resistances of the bacteria responsible for the symptoms. Many diseases of the respiratory tract are caused by viruses. Antibiotics are inefficient in such cases, and such patients are not cured of the infections.

The use of antiseptics and/or wound-healing promoting agents for external application to humans and animals is disclosed in our earlier patent EP 0 639 373. Specifically, liposome preparations of PVP-iodine are shown therein to be topically applicable to the external parts of the eye. These preparations generally take the form of a cream, an ointment, a lotion, a gel or a drop formulation.

Liposomes are well-known drug carriers and therefore the application of medicaments in liposomal form has been subject of investigation for quite some time. An overview concerning pulmonary delivery of liposome encapsulated drugs in asthma therapy is provided by the review "Pulmonary delivery of liposomes" (H. Schreier, in "Journal of Controlled Release", 24, 1993, p.209-223). The physicochemical characterization of liposome aerosols and also their therapeutic applications to the respiratory tract are shown therein. Drugs that have

been investigated for pulmonary delivery via liposomes include, e.g. anti-cancer agents, peptides, enzymes, anti-asthmatic and anti-allergic compounds and, as mentioned above, also antibiotics. The formulation of liposome aerosols or liposome powder aerosols using, for example a dry powder inhaler has also been described by H.

Schreier in "Formulation and in vitro performance of liposome powder aerosols" (S.T.P. Pharma Sciences 4, 1994, p.38-44).

Although a lot of attention has been paid to liposomes as drug carriers, as can be seen from the cited documents, there appears to be no prior art relating to liposomes and other particulates as carriers of anti-inflammatory, antiseptic and/or wound-healing promoting agents for applications in the body, especially in the lower respiratory tract, including the trachea, bronchi and alveoli.

Some of the prior art cited above is concerned with liposome preparations. It should be understood that alternative drug carriers of a similarly particulate character exist. These drug carriers can often -and also in the context of this invention- be used instead of liposomes and include microspheres (generally comprising lipophilic polymers), nanoparticles, "Large Porous Particles" and individually coated drug substance molecules, e.g. made by using pulsed laser deposition (PLD) techniques. These PLD methods can be used to apply coatings to drug powders and to modify surface properties and release rate to a variety of drug systems.

Where hereinafter reference is made to liposomes or particulate carriers, it is to be understood that this is to incorporate such alternative carriers, too.

It is known in the art that the administration of inhalable particles to the respiratory tract can be achieved by nebulization or aerosolization of the liposome, microsphere, Large Porous Particle, PLD or nanoparticle preparations or by dry powder inhalation of the respective preparation.

There appears to be a marked reluctance in the art, to apply disinfectants to interior parts of the body, except maybe in extreme cases of life-threatening septical complications.

Generally, antibiotic preparations appear to be preferred, even in view of their above-discussed disadvantages.

An object of the instant invention is to provide a well tolerated, easily applicable anti-inflammatory, antiseptic and/or wound-healing promoting preparation, which provides protracted release and protracted topical effect of the active agent in the lower respiratory tract.

According to the invention this object is attained in that the preparation comprises at least one anti-inflammatory, antiseptic and/or wound healing promoting agent in the form of a particulate carrier preparation, as defined in independent claim 1.

The invention further comprises a method of treating the lower respiratory tract, in humans and animals, as defined in independent claims 21 and 22.

The dependent claims define further advantageous embodiments of the invention.

In the context of this invention, anti-inflammatory agents are understood to include antiseptic agents, antibiotic agents, corticosteroids, and wound-healing agents, as defined below.

In the context of this invention, antiseptic agents are understood to include those disinfecting agents which are pharmaceutically acceptable and suitable for the treatment of the lower respiratory tract to the extent that they can be formulated in accordance with the invention.

More specifically, antiseptic agents include inter alia oxygen- and halogen-releasing compounds; metal compounds, e.g. silver and mercury compounds; organic disinfectants including inter alia formaldehyde-releasing compounds, alcohols, phenols including alkyl- and arylphenols as well as halogenated phenols, quinolines and acridines, hexahydropyrimidines, quaternary ammonium compounds and iminium salts, and guanidines.

Wound-healing agents comprise agents promoting granulation and epithelization such as dexpanthenol, allantoines, azulenes, tannines, and vitamine B-type compounds.

The invention is premised on the surprising fact that particulate carriers, especially liposomes, but also microspheres, nanoparticles and coated drug substance molecules, are highly suited as carriers for antiseptic agents, especially for povidone iodine, and for agents promoting the healing of wounds, for application to the lower respiratory tract.

The preparations according to this invention permit protracted release of the agent or agents, and provide an extended and topical activity at the desired locus of action by interaction with cell surfaces.

The invention is, another aspect, based on a further surprising and unexpected fact. It is well known in the art that the formation of new body tissues may cause problems. Thus, it is known that body tissue repair may be accompanied by the

formation of scar tissue, which can be functionally and/or cosmetically harmful, or at least undesirable. Hyperkeratosis and the uncontrolled proliferation of tissue may cause serious harm, leading to dysfunctions, and may of course also be cosmetically undesirable. After infections and inflammations, re-growing or healing tissue may cause neoplasms and intergrowth. It is thus well known in the art that in the curing of diseases, proper remodelling of tissue is not only desirable, but in fact necessary.

It has now been surprisingly found that the use of anti-inflammatory agents, singly or in combination with other such agents, leads to markedly less formation of undesirable body tissue in the course of tissue repair and other tissue growth processes. Thus, the formation of scar tissues is reduced, in skin but also in mucosa and in other tissues, such as muscle or inner organ tissues. Hyperkeratosis may be entirely suppressed, and intergrowth, or neoplasm formation in the curing of infective diseases is also highly reduced.

One object achieved by the invention is therefore concerned with improved tissue repair in the body. The invention achieves this by the application of anti-inflammatory agents, in the form of a particulate carrier preparation as defined in the independent claims.

The anti-inflammatory, antiseptic and/or wound-healing preparation can be administered to the respiratory tract by a nebulization agent loaded of the particulate carrier preparation, or by dry powder inhalation of the respective preparation. For example, a liposome preparation can be made by loading liposomes with PVP iodine in a conventional procedure.

It is also possible to compact the loaded liposomes, optionally together with auxiliary materials, such as low molecular sugars, preferably lactose, to a tightly

compacted solid medicament reservoir. This medicament stock can then be abraded or micronized or treated in other ways to yield the powder in particle form. The resulting liposome preparation can be administered by inhalation of the preparation in the form of a powder aerosol, as, for example, described in "Acute Effects of Liposome Aerosol Inhalation on Pulmonary Function in Healthy Human Volunteers" (Thomas et al., Preliminary report, Volume 99, 1991, p. 1268-1270). The pressures for preparing the tightly compacted solid medicament stock are preferably in the range of from 50-500 MPa. Such medicament stock is described in WO 94/14490 and a device for administration is disclosed in WO 93/24165.

The nature or constitution of the liposomes is generally not critical. The liposome preparation as, for example, described in EP 0 639 373 can be administered by inhalation as an aerosol. The disclosure of EP 0 639 373 is incorporated by reference.

The preparations according to this invention apparently do not only contain the active agent, like povidone iodine, encapsulated in the particulate carrier, especially in liposomes. It seems that there is also some amount of agent which is not contained inside the carrier. The preparations according to the invention often show a marked initial effect which is observed in addition to the slower, protracted release of the active agent from the carrier. This effect is especially observed where the carrier comprises liposomes. Without wishing to be bound to any theoretical explanation, it is presently assumed that in addition to active agent encapsulated inside the liposomes, some active agent is present outside of the liposomes, and probably loosely bound to the outer surfaces of the liposomes. This could be due to association of active agent molecules with the liposomal membrane, or it could be due to active agent molecules forming a layer on the liposomal surface, which layer partly or even fully coats the liposome externally. The type and amount of this initial agent effect can e.g. be influenced by choice

of the concentration parameters.

The amphiphilic substances generally known in prior art to form liposome membranes can be employed in the context of the invention as long as they are pharmaceutically acceptable for the intended application. Presently, liposome forming systems comprising lecithin are preferred. Such systems can comprise hydrogenated soy bean lecithin besides cholesterol and disodium succinate-hexahydrate; it is presently specificially preferred to use hydrogenated soy bean lecithin as the sole membrane-forming agent.

The known prior art methods for forming liposome structures are described in the documents cited above and can generally be used in the context of the invention. Broadly, these methods comprise mechanical agitation of a suitable mixture containg the membrane forming substance and water or an aqueous solution. Filtration through suitable membranes is preferred in forming a substantially uniform liposome size.

The average size of the liposomes according to this invention can vary over a broad range, generally from about 1 to about 50 µm, preferably in the range of 1 and 30 µm diameter. For solutions, smaller average diameters, e.g. diameters of about 100 nm, may be more suitable.

The liposomes according to this invention have a substantially uniform size in the range between about 20 and 30 µm diameter for application to the trachea, in the range between about 10 and 20 µm diameter for application to the bronchi and between about 1 and 6 µm, especially between 2 and 5 µm, diameter for application to the alveoli.

Where alternative particulate carriers are used, they are generally prepared as known in the art. Thus, microspheres which are used to deliver a very wide range of therapeutic or cosmetic agents, are made as described for example in WO 95/15118.

Nanoparticles may in some cases be used, provided that they can be loaded with a sufficient amount of active agent and can be administered to the lower respiratory tract according to this invention. They can be prepared according to the methods known in the art, as e.g. described by Heyder (GSF München) in "Drugs delivered to the lung", Abstracts IV, Hilton Head Island Conference, May 1998.

Methods using a pulse laser deposition (PLD) apparatus and a polymeric target to apply coatings to drug powders in a short non-aqueous process are also suitable for the formation of particulate preparations according to this invention. These have e.g. been described by Talton et al., "Novel Coating Method for Improved Dry Delivery", Univ. of Florida UF 1887 (1998).

A further suitable delivery system employs Large Porous Particles as disclosed by David A. Edwards et al. in "Large Porous Particles for Pulmonary Drug Delivery" (Science, 20. June 1997, Vol. 276, p. 1868-1871). The average size of Large Porous Particles according to this invention can e.g. be in the range of between about 5 and 20 μm diameter for application to the alveoli.

Preferred anti-inflammatory agents comprise antiseptic agents, antibiotics, corticosteroids and wound-healing promoting agents, as single substances or in combination with each other.

Preferred antiseptic agents comprise the well-known pharmaceutical substances providing fast effect, a broad range of activity, low systemic toxicity and good

tissue compatibility. They can e.g. be selected from the group comprising metal compounds, phenolic compounds, detergents, iodine and iodine complexes. A specifically preferred antiseptic agent is povidone iodine.

Preferred agents promoting the healing of wounds comprise substances which have been described in the literature for such application. Preferred such agents include substances known to promote epithelisation. These include vitamins, specifically from the vitamin B group, allantoin, some azulenes etc.

Some presently highly preferred embodiments of the invention comprise anti-inflammatory agents or combinations of such agents which show beneficial effects in tissue repair, especially with respect to functional and cosmetic tissue remodelling. In these embodiments, the active agent is often an antiseptic, such as PVP-iodine, or an antibiotic.

In preferred embodiments, the invention's preparations containing anti-inflammatory, especially antiseptic and/or wound-healing promoting agents can comprise further agents such as anaesthetic agents. Inventive preparations can also contain customary further agents, including adjuvants and additives, antioxidants, conserving agents or consistency-forming agents such as viscosity adjusting additives, emulgators etc.

Generally, the concentrations in the preparation, particle sizes, active agent loadings etc. will be selected for such alternative carriers to correspond basically to the parameters discussed herein with respect to liposome preparations. Selecting and providing such parameter based inter alia on straightforward experimentation, is well within the skill of an ordinary worker experienced in this art.

A presently highly preferred use of the inventive liposome preparations is in the treatment of infections of the lower respiratory tract, including trachea, bronchi and alveoli, especially when the liposome preparations contain povidone iodine. Also in this indication, the inventive antiseptic preparations, especially those containing PVP iodine, have the great advantage of not causing resistances and lead to much less allergic reactions, while permitting a very cost-efficient therapy with a broad spectrum of effect. A povidone iodine liposome preparation according to this invention is e.g. effective against viruses. Further, a liposome preparation of a microbicidal agent such as povidone iodine provides protracted release of the agent from liposomes delivering the agent to the pulmonary regions, for example to the alveolar regions of the lung. This leads to extended effect of the antimicrobial substance, and thus less frequent application, as compared with the customary antiseptic solution preparations.

The present invention is also useful in the treatment of infectious diseases or for alleviation of diseases such as HIV infections which are accompanied by opportunistic infections. Also patients having a suppressed immune system, for example, after organ transplants, can be treated according to the invention. In particular, acute and chronical bronchitis, pneumonia, bronchiectasia, cystic fibrosis, diphtheria, tuberculosis can be treated with the povidone iodine preparation according to the invention.

Further highly preferred use is in tissue repair, especially in functional and cosmetic tissue remodelling.

Preparations according to this invention can take a variety of forms, which are suitable for administration via the lower respiratory tract, including pharmaceutically acceptable solid or liquid formulations, which are suitable for the generation of inhalable particles. Preparations according to this invention can be

therefore in the form of (powder) aerosol or in the form of a compacted solid medicament reservoir, preferably a ring tablet, more preferably a gelatine capsule, a powder, a spray, an emulsion, a dispersion, a suspension or even a solution containing the carrier and agent or agents.

Generally, the amount of active agents in an inventive preparation will be determined by the desired effect, on the one hand, and the carrying capacity of the carrier preparation for the agent, on the other hand.

For inventive preparations with large amounts of active agents or high dosages of active agent, nebulized preparations or aerosols are preferred to powders or powder aerosols. Broadly, the amount of active agent in an inventive carrier preparation can range in concentrations between the lower limit of effectiveness of the agent and the maximum loading of the agent in the respective carrier preparation.

More specifically, for an antiseptic agent, such as povidone iodine, a solution or dispersion in an inventive carrier preparation, especially where the carrier is a liposome preparation, can contain between 0.1 and 10 g of agent in 100 g of preparation. Such a preparation will then typically contain between 1 and 5 g of liposome membrane-forming substance, especially lecithin, per 100 g of preparation.

An inventive aerosol or spray preparation will often comprise up to 50 mg, but could comprise up to and above 100 mg of liposomal active agent formulation and can, for example, be administered by 5 spray doses, each containing 20 mg of liposomal active agent formulation.

The preparation will typically comprise at least 10 % wt of active agent such as PVP-iodine in the loaded liposomes (or alternative carrier particles), but may comprise up to 50 wt.-% or even more of active agent. Where the active agent is PVP-iodine, the amount of available iodine will generally be about 10 wt.-% (based on PVP-iodine).

More specific formulations are notable from the embodiment examples.

The features and advantages of this invention will become notable in more detail from the ensuing description of preferred embodiments. In these embodiments, which include a best mode, povidone iodine is exemplified as an antiseptic agent and liposomes are chosen as the carrier. This should, however, not be construed as a restriction of this invention to antiseptic agents or, among antiseptic agents, to povidone iodine, and/or to liposomes as the carrier, although such preparations are specifically preferred.

One preferred method for producing the invention's liposomes can generally be described as follows:

The lipid membrane-forming components, e.g. lecithin, are dissolved in a suitable solvent such as chloroform or a 2:1 mixture of methanol and chloroform and are filtered under sterile conditions. Then, a lipid film is produced on a sterile high surface substrate, such as glass beads, by controlled evaporation of the solvent. In some cases, it can be quite sufficient to form the film on the inner surface of the vessel used in evaporating the solvent, without using a specific substrate to increase the surface.

An aqueous system is prepared from electrolyte components and the (one or more) active agents to be incorporated in the liposome preparation. Such an aqueous

system can e.g. comprise 10 mmol/l sodium hydrogen phosphate and 0.9 % sodium chloride, at pH 7.4; the aqueous system will further comprise at least the desired amount of the active agent, which in the embodiment examples is povidone iodine. Often, the aqueous system will comprise an excess amount of agent or agents.

The liposomes are generally formed by agitating said aqueous system in the presence of said film formed by the lipid components. At this stage, further additives can be added to improve liposome formation; e.g. sodium cholate can be added. Liposome formation can also be influenced by mechanical action such as pressure filtration through e.g. polycarbonate membranes, or centrifuging. Generally, the raw liposome dispersion will be washed, e.g. with electrolyte solution as used in preparing the above-described solution of the active agent.

When liposomes with the required size distribution have been obtained and washed, they can be redispersed in an electrolyte solution as already described, often also comprising sugars such as saccharose or a suitable sugar substitute. The dispersion can be freeze-dried, and it can be lyophilysed. It can, prior to use, be reconstituted by addition of water and suitable mechanical agitation at the transition temperature of the lipid component, which for hydrogenated soy bean lecithin is e.g. 55°C.

In the following Examples, hydrogenated soy bean lecithin (EPIKURON (TM) 200 SH obtainable from Lukas Meyer, Germany or PHOSPOLIPON (TM) 90 H obtainable from Nattermann Phospholipid GmbH, Germany) was used. However, other pharmaceutically acceptable liposome membrane-forming substances can be used instead, and the person skilled in the art will find it easy to select suitable alternative liposome forming systems from what is described in prior art.

Embodiment Example I

In a 1000 ml glass flask, provided with glass beads for increased surface, 51.9 mg cholesterol and 213 mg hydrogenated soy bean lecithin were dissolved in a sufficient amount of a mixture of methanol and chloroform in a 2:1 ratio. The solvent was then evaporated under vacuum until a film was formed on the inner surface of the flask and on the glass beads.

2.4 g PVP iodine (containing about 10 % available iodine) were separately dissolved in 12 ml water.

Again in a separate vessel, 8.77 g sodium chloride and 1.78 g $Na_2HPO_4 \cdot 2H_2O$ were dissolved in 400 ml water. Further water was added up to a total volume of 980 ml, and then, approximately 12 ml 1N hydrochloric acid were added to adjust pH to 7.4. This solution was then topped up with water to exactly 1000 ml.

In a fourth vessel, 900 mg saccharose and 57 mg disodium succinate were dissolved in 12 ml water.

The PVP iodine solution was then added to the lipid film in the flask and the mixture was shaken until the film dissolved. The resulting liposome formulation was separated from the hydrated lipids in the flask. The product was centrifuged and the supernatant liquid was discarded. The saccharose solution was added ad 12 ml and the product was again centrifuged. Afterwards the supernatant liquid was again discarded. At this stage, a further washing step, using the saccharose solution or the sodium chloride buffer solution could be carried out.

After the last centrifugation step and discarding of the supernatant, 12 ml sodium chloride buffer solution was added, and the liposomes were homogenously

distributed therein. The product was then distributed into vials each containing 2 ml liposome dispersion, and the vials were then subjected to a freeze-drying step.

After the freeze-drying, each vial comprised about 40 mg solids.

The method of Embodiment Example I has a minor disadvantage in that the PVP iodine solution used, due to the high percentage of solids, is rather viscous and thus more difficult to handle.

Embodiment Example II

In a 2000 ml flask provided with glass beads to increase surface, 173 mg hydrogenated soy bean lecithin and 90 mg disodium succinate were dissolved in approximately 60 ml of a methanol/chloroform mix in a 2:1 ratio. The solvent was removed under vacuum until a film was formed.

4 g PVP iodine (10 % available iodine) were dissolved in 40 ml of the sodium chloride buffer solution described in Embodiment Example I, and were added to the lipid film in the flask. The flask was then shaken until the film dissolved and liposomes were formed.

The product was centrifuged and the supernatant liquid was discarded.

To the thus produced liposome pellet, further 40 ml sodium chloride buffer solution was added, and the centrifuging step was repeated. The supernatant was again discarded. At this stage, the washing step could be repeated where necessary.

After the final centrifuging and decanting step, 40 ml sodium chloride buffer solution was again added to the precipitated liposomes. The homogenous dispersion was then distributed into vials, each vial containing about 2 ml liposome dispersion, and the vials were then subjected to a freeze-drying step. This produced approximately 200 mg freeze-dried solids per vial.

Like that of Embodiment Example I, the above-described method uses a hydrating step after film formation in the presence of organic solvents and aims at inclusion rates of 5 to 15 %. These methods generally produce rather large and often multi-lamellar liposomes.

The above-described methods can be modified by a high pressure filtering step through a suitable membrane such as a polycarbonate membrane after the raw liposomes have been formed or after any of the subsequent washing steps or directly by using high pressure homogenisation. This produces much smaller, unilamellar liposomes at increased amounts of encapsulated agent.

Instead of high pressure homogenisation, other prior art methods known to provide small uniform sized liposomes can be employed.

Embodiment Example III

A gelatine capsule, which is suitable for the generation of inhalable particles, was prepared from 20 g of povidone iodine liposomes containing leophilised (?????) material according to the above-mentioned general preparation method and 20 mg lactose by applying pressures of up to 500 MPa. From the obtained hard capsule a powder or powder aerosol was generated by abrading methods using a powder inhaler (Orbital-Inhaler by Brin Tech International Ltd.

It is also possible to prepare embodiments similar to those described above, which comprise an agent capable of promoting the healing of wounds insteads of, and not in addition to, the antiseptic agent, such as e.g. povidone iodine disclosed in the above embodiment examples. Presently, it is however preferred to use a wound healing promoting agent (if at all) in addition to an antiseptic agent.

For application of the inventive preparations to a patient, known systems can be used, such as inhalers, powder inhalers, two-chamber gas pressure packs, aerosol spray dispensers, nebulizers, compressors, etc.

Embodiment Example IV

Liposomic preparations were aerosolized via an air-driven nebulizer. The output and aerosol characteristics of liposomes with the nebulizer have been previously described. The resulting droplets had a mass medium aerodynamic diameter of about 2.4 μm and are therefore suitable for deposition in the alveolar region.

Using inventive preparations efficiency tests were then carried out, as follows:

Test I

This was an in-vitro-test of the bactericidal effect provided by an inventive povidone iodine liposome preparation. The test was based on the quantitative suspension test as described in "Richtlinien der Deutschen Gesellschaft für Hygiene und Mikrobiologie", 1989. In this test, the bactericidal agent is used to kill staphylococcus aureus (ATCC 29213), a major problem in hospital hygiene.

The liposome preparation used was that of Embodiment Example I. At different contact times between 1 und 120 minutes, the minimum concentration of the preparation in water was determined which was capable of killing the

staphilococci.

The results are shown in Table 1.

TABLE I

Contact Time (Minutes)	Bactericidal Concentration
1, 2, 3, 4	≥ 0.060 %
5, 30, 60	≥ 0.015 %
120	≥ 0.007 %

The results show that at short contact times (between 1 and 4 minutes) the bactericidal concentration is as low as 0.06 % and that at long contact times (120 minutes) the bactericidal concentration can be as low as 0.007 %.

Test II

The virucidal and chlamydicidal activity of liposomal PVP-iodine has been studied, in cell cultures, by Wutzler et al., 9th European Congress for Clinic Microbiology and Infection Diseases, Berlin, March 1999. In cell cultures, liposomal PVP-iodine is highly effective against herpes simplex virus type 1 and adenovirus tpye 8, while the long-term cytotoxicity experiments indicated that the liposomal form is better tolerated than aqueous PVP-iodine by the majority of cell lines tested. PVP-iodine in liposomal form is not genotoxic.

Test III

A 3% PVP-iodine hydrogel liposomal preparation was compared with a 3% PVP-iodine ointment, where the active agent was not in liposomal form. The agent

was applied to standardized in vitro cultures of rat skin and peritoneal explants, as a screening for tissue compatibility of skin and wound antiinfectives.

The growth rate of the cultured explants was studied after 30 minutes exposure and incubation with a test substance.

Again, the substantially better toleration of the liposomal preparation was clearly shown in the results, in terms of peritoneum growth rate and skin growth rate.

With the ointment, the peritoneum growth rate reached 85%, and the skin growth rate reached 90%; with the liposomal hydrogel formulation, the peritoneum growth rate was 96%, and the skin growth rate was 108%; these values are to be compared with 100% values in a control test using Ringer's solution as the agent.

Claims

1. A process for the manufacture of a pharmaceutical preparation for the application of antiseptic agents and/or agents which promote the healing of wounds to the lower respiratory tract,
characterised in that the preparation contains at least one of said agents combined with a particulate carrier.

2. The process of claim 1,
characterised in that said particulate carrier comprises at least one of a liposome preparation, a microsphere preparation, a nanoparticle preparation, a Large Porous Particle preparation or a laser-pulse polymer coated molecule preparation.

3. The process according to claim 1 or 2,
characterised in that at least the greatest part of said agent is encapsulated inside the carrier, especially a liposome or microsphere carrier.

4. The process of any one of claims 1 to 3,
characterised in that the antiseptic agent is selected from oxygen- and halogen-releasing compounds; metal compounds, such as silver and mercury compounds; organic disinfectants including inter alia formaldehyde-releasing compounds, alcohols, phenols including alkyl- and arylphenols as well as halogenated phenols, quinolines and acridines,

hexahydropyrimidines, quaternary ammonium compounds and iminium salts, and guanidines.

5. The process according to claim 4,

characterised in that the antiseptic agent is selected from the group comprising metal compounds such as mercury compounds, phenol derivatives such as thymol, eugenol and hexachlorophene, iodine and iodine complexes.

6. The process according to claim 5,

characterised in that the antiseptic agent is povidone iodine.

7. The process according to any one of claims 1 to 6,

characterised in that the wound-healing promoting agent is selected from agents promoting granulation and epithelization such as dexpanthenol, allantoines, azulenes, tannines, compounds from the vitamin B series, or similarly acting agents.

8. The process according to any one of the preceding claims,

characterised in that the preparation contains at least one antiseptic and at least one wound-healing promoting agent.

9. The process according to any one of the preceding claims, characterised in that the carrier particles, especially liposomes, have a substantially uniform size in the range between about 1 and about 50 μm, preferably in the range between about 1 and about 30 μm.

10. The process according to claim 9, characterised in that the carrier particles, especially liposomes, have a substantially uniform size in the range between about 20 and 30 μm diameter for application to the trachea, in the range between about 10 and 20 μm diameter for application to the bronchi and between about 1 and 6 μm, especially between 2 and 5 μm, diameter for application to the alveoli.

11. The process according to any one of the preceding claims, characterised in that the carrier, especially liposome, preparation releases the agent over an extended time period, preferably an extended time period of several hours duration.

12. The process according to claim 11, characterised in that the carrier, especially liposome, preparation releases the agent at approximately the same release rate over the release time period.

13. The process according to any one of the preceding claims, characterised in that the preparation additionally comprises at least one anaesthetically active agent.

14. The process according to any one of the preceding claims, characterised in that the preparation contains additives and adjuvants such as conserving agents, antioxidants and consistency-forming additives.

15. The process according to any one of claims 1 to 14, the preparation being in a suitable form for administration via the lower respiratory tract comprising the active-agent loaded carrier, especially in the form of liposomes, preferably in the form of an aerosol, especially in the form of a powder aerosol.

16. The process according to any one of claims 1 to 14, the preparation being in the form of a compacted solid medicament reservoir, preferably a ring-tablet, more preferably a gelatin capsule, a powder, a spray, an emulsion, a dispersion, a suspension or a solution containing the carrier and agent or agents in a pharmaceutically acceptable solid or liquid formulation, which is suitable for the generation of inhalable particles.

17. The process according to any one of the preceding claims, the preparation being in a suitable form for administration via the lower respiratory tract, which comprises:

a) liposomes comprising a pharmaceutically acceptable liposome membrane forming substance; and

b) a 0.1 to 2 % PVP iodine solution (at approximately 10 % available iodine in the PVP iodine complex) at least most of which is encapsulated by said liposome membranes,

wherein the liposomes are of substantially uniform size between about 1 and about 50 µm, and, in case, the formulation additionally comprises customary additives, adjuvants and auxiliary substances of a pharmaceutical formulation.

18. The process according to claim 17,

characterised in that the liposomes are of substantially uniform size, in the range between about 20 and 30 µm diameter for application to the trachea, in the range between about 10 and 20 µm diameter for application to the bronchi and between about 1 and 6 µm diameter, preferably between about 2 and 5 µm diameter, for application to the alveoli.

19. The process according to any one of claims 1 to 18, wherein the preparation is suited for the treatment of infectious diseases or alleviation of diseases such as HIV infections which are accompanied by opportunistic infections

or a suppressed immune system.

20. The process according to any one of claims 1 to 18, wherein the preparation is suited for the treatment of acute and chronic bronchitis, pneumonia, bronchiectasia, cystic fibrosis, diphtheria and/or tuberculosis.

21. The process according to any one of claims 1 to 20, wherein the preparation is suited for functional and cosmetic tissue remodelling and repair treatments.

22. A method of preventing or treating infections of the human or animal lower respiratory tract, by applying, to said tract, a pharmaceutical preparation comprising at least one antiseptic agent and/or wound-healing promoting agent, said agent being combined with a particulate carrier in said preparation.

23. A method of functional and cosmetic tissue remodelling and repair in the human or animal lower respiratory tract, by applying, to said tract, a pharmaceutical preparation comprising at least one anti-inflammatory especially antiseptic and/or wound-healing promoting agent combined with a particular carrier.

24. The method of claim 22 or 23, wherein said carrier comprises at least one of a liposome preparation, a microsphere preparation, a nanoparticle preparation, a Large Porous Particle preparation, or a laser-pulse polymer coated molecule preparation.

25. The method of claim 22 or 23, wherein at least the greatest part of said agent is encapsulated inside the carrier, especially a liposome or microsphere carrier.

26. The method of claim 23, wherein the anti-inflammatory agent is selected from antiseptic agents, antibiotics, corticosteroids and wound-healing promoting agents.

27. The method of claim 22 or 23, wherein the antiseptic agent is selected from oxygen- and halogen-releasing compounds; metal compounds, such as silver and mercury compounds; organic disinfectants including inter alia formaldehyde-releasing compounds, alcohols, phenols including alkyl- and arylphenols as well as halogenated phenols, quinolines and acridines, hexahydropyrimidines, quaternary ammonium compounds and iminium salts, and guanidines.

28. The method of claim 22 or 23, wherein the antiseptic agent is selected from the group comprising metal compounds such as mercury compounds phenol derivatives such as thymol, eugenol and hexachlorophene, iodine and iodine complexes.

29. The method of claim 22 or 23, wherein the antiseptic agent is povidone iodine.

30. The method of claim 22 or 23, wherein the wound-healing promoting agent is selected from agents promoting granulation and epithelization such as dexpanthenol, allantoines, azulenes, tannines, compounds from the vitamin B series or similarly acting agents.

31. The method of claim 22 or 23, wherein the preparation contains at least one antiseptic and at least one wound-healing promoting agent.

32. The method of claim 22 or 23, wherein the carrier particles, especially liposomes, have a substantially uniform size in the range between about 1 and about 50 μm, preferably in the range between about 1 and about 30 μm.

33. The method of claim 32, wherein the carrier particles, especially liposomes, have substantially uniform size in the range between about 20 and 30 µm diameter for application to the trachea, in the range between about 10 and 20 µm diameter for application to the bronchi and between about 1 and 6 µm diameter, especially between 2 and 5 µm, for application to the alveoli.

34. The method of claim 22 or 23, wherein the carrier, especially liposome, preparation releases the agent over an extended time period, preferably an extended time period of several hours duration.

35. The method of claim 22 or 23, wherein the carrier, especially liposome, preparation releases the agent at approximately the same release rate over the release time period.

36. The method of claim 22 or 23, wherein the preparation additionally comprises at least one anaesthetically active agent.

37. The method of claim 22 or 23, wherein the preparation contains additives and adjuvants such as conserving agents, antioxidants and consistency-forming additives.

38. The method of claim 22 or 23, the preparation being in a suitable form for administration via the lower respiratory tract comprising the active-agent loaded carrier, especially in the form of liposomes, preferably in the form of an aerosol, especially in the form of a powder aerosol.

39. The method of claim 22 or 23, the preparation being in the form of a compacted solid medicament reservoir, preferably a ring-tablet, more preferably a gelatine capsule, a powder, a spray, an emulsion, a dispersion, a suspension or a solution containing the carrier and agent or agents in a pharmaceutically acceptable solid or liquid formulation, which is suitable for the generation of inhalable particles.

40. The method of claim 22 or 23, the preparation being in a suitable form for administration via the lower respiratory tract, which comprises:

a) liposomes comprising a pharmaceutically acceptable liposome membrane forming substance; and

b) a 0.1 to 2 % PVP iodine solution (at approximately 10 % available iodine in the PVP iodine complex) at least most of which is encapsulated by said liposome membranes,

wherein the liposomes are of substantially uniform size between about 1 and about 50 μm, and, in case, the formulation additionally comprises customary additives, adjuvants and auxiliary substances of a pharmaceutical formulation.

41. The method of claim 22 or 23, wherein the liposomes are of substantially uniform size, between about 20 and 30 μm diameter for application to the trachea, between about 10 and 20 μm diameter for application to the bronchi and between about 1 and 6 μm, preferably between about 2 and 5 μm diameter, for application to the alveoli.

42. The method of claim 22 or 23, wherein the preparation is suited for the treatment of infectious diseases or alleviation of diseases such as HIV infections which are accompanied by opportunistic infections or a suppressed immune system.

43. The method of claim 22 or 23, wherein the preparation is suited for the treatment of acute and chronic bronchitis, pneumonia, bronchiectasia, cystic fibrosis, diphtheria and/or tuberculosis.

INTERNATIONAL SEARCH REPORT

Internat' I Application No
PCT/EP 99/03681

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/127

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 639 373 A (EUROCELTIQUE) 22 February 1995 (1995-02-22) claims 1-18 ---	1-43
A	EP 0 613 685 A (GONZALEZ ENSENAT, PEDRO, ET AL.) 7 September 1994 (1994-09-07) claim 1 column 4, line 19 - line 26 ---	1-43
A	EP 0 509 338 A (MERZ & CO.) 21 October 1992 (1992-10-21) claims 1,9 example 7 --- -/--	1-43

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 October 1999	09/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Ventura Amat, A

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internat' l Application No
PCT/EP 99/03681

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 117, no. 10, 7 September 1992 (1992-09-07) Columbus, Ohio, US; abstract no. 97244, GILBERT, BRIAN E. ET AL: "Aerosolized liposomal amphotericin B for treatment of pulmonary and systemic Cryptococcus neoformans infections in mice" XP002119931 abstract & ANTIMICROB. AGENTS CHEMOTHER. (1992), 36(7), 1466-71 ,1992,	1-3, 9-12, 14-16, 18-26, 32-35, 37-39, 41-43

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte. onal application No.
PCT/EP 99/03681

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 22-43 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat' Application No
PCT/EP 99/03681

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